Outcomes of Bacteremia in Burn Patients Involved in Combat Operations Overseas

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BACKGROUND: Burn patients constitute approximately 5% of casualties injured in support of US military operations in Iraq (Operation Iraqi Freedom [OIF]) and Afghanistan (Operation Enduring Freedom [OEF]). Since the onset of these conflicts, there have been numerous casualties infected with multidrug-resistant bacteria. It is currently unclear if bacteremia with these multidrug-resistant organisms in OIF/OEF burn casualties is associated with increased mortality.

STUDY DESIGN: We performed a retrospective cohort study of all patients admitted to the US Army Institute of Surgical Research burn center from January 2003 to May 2006 to evaluate bacteremia in our burn-patient population.

RESULTS: One hundred twenty-nine of 1,258 patients admitted to the burn center became bacteremic during their hospitalization. Of these, 92 had bacteremia with the top four pathogens in our burn center, ie, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter calcoaceticus-baumannii* complex, and *Staphylococcus aureus*. Presence of any bacteremia was associated with mortality and increased ventilator days. Bacteremia with *K pneumoniae* was associated with a statistically increased mortality and a prolonged ventilator course relative to all other pathogens.

CONCLUSIONS: Casualties of OIF/OEF with burn injuries did not have different outcomes than patients whose burns were not associated with military operations. Bacteremia, especially with a multidrug-resistant organism, causes increased mortality in burn patients. Of all the pathogens causing bacteremia, *K pneumonia* appears to have the greatest impact on mortality. (J Am Coll Surg 2008;206:439–444. © 2008 by the American College of Surgeons)

Burn injuries have been noted in approximately 5% of US military casualties evacuated during operations during Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), mostly secondary to explosive devices.[1] In modern-day burn units, the majority of burn-related deaths result from septic shock, with bacteremia being a common infection.[2,3] The most frequently identified pathogens associated with bacteremia are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Since the onset of OIF/OEF, infections with other bacteria, particularly multidrug-resistant bacteria, have developed in numerous casualties. Infections with *Acinetobacter calcoaceticus-baumannii* complex (Acb) have been receiving attention in health care facilities recently, including military facilities and burn centers.[4] Our earlier work did not find an association of attributable mortality with Acb infection among burn combat casualties.[4] An outcomes assessment of patients burned in support of OIF/OEF versus those not burned during OIF/OEF revealed similar mortality rates when adjusted for age. This assessment did not evaluate outcomes as they relate to infection.[1] We performed a retrospective cohort study of all patients admitted to the US Army Institute of Surgical Research (USAISR) burn center from January 2003 to May 2006, to evaluate the impact of bacteremia in this patient population. Our goals were to determine the attributable mortality of the most common pathogens, their associated antimicrobial-resistance patterns, and the role of being injured in support of OIF/OEF.

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Abbreviations and Acronyms

Acb = *Acinetobacter calcoaceticus-baumannii* complex
ESBL = extended spectrum β-lactamase
IQR = interquartile range
ISS = Injury Severity Score
MDRO = multidrug-resistant organisms
OEF = Operation Enduring Freedom
OIF = Operation Iraqi Freedom
TBSA = total body surface area
USAISR = US Army Institute of Surgical Research

METHODS

This was a retrospective chart review performed in a 40-bed burn center at a 224-bed Level I trauma center that serves both the Department of Defense and local civilian populations. Burn unit electronic medical records from January 2003 to May 2006 were reviewed to identify all admissions during that time period. For each admission the following demographics were collected: age, OIF/OEF versus non-OIF/OEF (includes civilian patients burned in the US or military patients burned somewhere else other than Iraq or Afghanistan), percent total body surface area (TBSA) burned, Injury Severity Score (ISS), number of ventilator days, and survival to discharge.

The microbiology database was then searched for all patients in the burn unit with bacteremia. After determining that the top four bacteremia pathogens in our burn center were *P aeruginosa*, *Klebsiella pneumoniae*, Acb, and *S aureus*, patients were classified as having a single episode of bacteremia; multiple episodes of bacteremia with the same organism; or bacteremia with more than one organism to include one of the top pathogens and another species during their stay in the burn ICU, which can include a species not included in the top four pathogens. In addition, a single patient might have had bacteremia with more than one of the top four pathogens during their admission. Bacteremia with more than one organism did not have to occur concomitantly in the same blood culture bottle. A patient was considered to have multiple episodes of bacteremia with the same organism if that organism grew in another blood culture more than 2 weeks from the original positive blood culture. A length of 2 weeks was chosen because, for the top four organisms, 2 weeks of IV antibiotics is generally used to treat the bacteremia.

Organism susceptibility patterns from our institution's microbiology database (VITEK; bioMerieux VITEK Inc) were reviewed for blood culture isolates of the top four pathogens to assess for drug resistance. Isolates were coded as multidrug-resistant organisms (MDRO) as follows: *P aeruginosa* and Acb susceptible to only one drug class, not including colistin or minocycline; *K pneumoniae* that were extended spectrum β-lactamase (ESBL) producers; and *S aureus,* which were methicillin-resistant.

Patients with known chemical burns, toxic epidermal necrolysis, incomplete electronic records, or were still admitted at the time of data collection, were excluded.

Burn care at our facility emphasizes early wound excision and skin grafting with perioperative antibiotics consisting of vancomycin and amikacin administered on the day of operation. Patients are maintained in individual rooms with contact isolation and strictly enforced hygiene practices. Varying topical antimicrobial creams were applied during hospitalizations at the discretion of the attending staff. All burn ICU patients had central venous and arterial lines in place, with replacement of central lines every 3 days and arterial lines every 7 days. Blood cultures were obtained through central venous catheters, arterial lines, or peripheral phlebotomy.

Survival to discharge and number of ventilator days were analyzed separately as outcomes of interest. Categorical variables were compared using chi-square test, and continuous variables were compared using the Student's *t*-test or appropriate nonparametric test for non-normally distributed data. Multivariate analysis was performed using binary logistic regression. Variables found to be pronounced on univariate analysis were included in the model and analyzed using the backward conditional method. All statistical tests were performed using SPSS software (version 15.0; SPSS Inc). Statistical significance was considered as $p < 0.05$.

Table 1. Comparative Demographics of Bacteremic Versus Nonbacteremic Burn Patients, January 2003 to May 2006

	Bacteremic (n = 92)	Nonbacteremic (n = 1,058)	p Value
Age (y), median (IQR)	30 (22–43)	29 (22–45)	0.94*
TBSA burned (%), median (IQR)	45 (30.5–65.5)	7.5 (3–15)	<0.001*
ISS, median (IQR)	25 (25–34)	4 (1–9)	<0.001*
Mechanic ventilation, n (%)	85 (92)	243 (23)	<0.001
OIF/OEF casualty, n (%)	51 (55)	363 (34)	<0.001

*Kolmogorov-Smirnov Test.
IQR, interquartile range; ISS, Injury Severity Score; OEF, Operation Enduring Freedom (combat operations in Afghanistan); OIF, Operation Iraqi Freedom; TBSA, total body surface area.

RESULTS

In total, 1,258 patients were admitted to the USAISR burn center during the time period of January 2003 to May 2006. Of these, 1,189 patients were included in the study (Table 1). One hundred twenty-nine had bacteremia during their hospital stay. Ninety-two of 129 had

Table 2. Most Common Pathogens Recovered from Blood of 92 Burn Patients, January 2003 to May 2006

Organism	n*	No. of isolates	Multidrug-resistant isolates	
			n	%
Pseudomonas aeruginosa	36	96	38	39.6
Klebsiella pneumoniae	34	83	59	71.1
Acinetobacter calcoaceticus-baumannii complex	44	67	45	67.2
Staphylococcus aureus	23	37	28	75.7

*Does not add up to 92, as numerous patients had more than one episode of bacteremia and a single patient might have had bacteremia with more than one of the top four pathogens during their admission.

bacteremia with at least one of the top four organisms (Table 2). The other bacteria recovered included 30 isolates of *Serratia marcescens*, 23 isolates of *Enterobacter* spp 22 isolates of coagulase-negative *Staphylococcus*, 12 isolates of *Streptococcus* spp (6 *viridans* and 6 group D), 9 isolates of *Enterococcus* spp (5 *faecium* and 4 *faecalis*), 8 isolates of *Escherichia coli*, 6 isolates of *Proteus mirabilis*, 5 isolates of *Stenotrophomonas* spp, and 3 or fewer isolates of *Corynebacterium* spp, *Bacillus* spp, *Aeromonas hydrophilia, Propionibacterium acnes, Clostridium clostridiiforme, Pseudomonas fluorescens*, *Pseudomonas putida, Chryseobacterium gleum, Citrobacter koserii, Acinetobacter junii, Micrococcus, Providencia stuartii, Yersinia kristensenii*, and *Salmonella* spp.

Overall, burn patients with bacteremia had higher TBSA and ISS, and were more likely to require mechanic ventilation compared with nonbacteremic patients (Table 1). In addition, bacteremic patients were more likely to be OIF/OEF casualties. The most common bacteremia pathogens found in the USAISR burn unit isolates were *P aeruginosa*, *K pneumoniae*, Acb, and *S aureus*, with the majority of isolates meeting criteria as an MDRO. The majority of *P aeruginosa* isolates was classified as being non-MDRO. Our definition for *P aeruginosa* MDRO was intentionally strict, given our patient population and historic antimicrobial-resistance patterns within the burn unit.

For the first analysis, bacteremic patients were compared with nonbacteremic patients with in-hospital mortality as one of the outcomes of interest. Presence of any bacteremia was an independent risk factor for mortality on univariate (relative risk = 18.6; $p \leq 0.01$) and multivariate analysis (relative risk = 2.60, $p = 0.02$) (Table 3). Age, ISS, and TBSA were also found to be notably associated with mortality, both on univariate and multivariate analysis. The nature of the patient's injury—OIF/OEF versus non-OIF/OEF—did not affect mortality.

For the second analysis, only bacteremic patients were included, to determine the pathogens with the most substantial effects on mortality. Among the 92 bacteremic patients, the following risk factors were associated with mortality on univariate analysis: age, ISS, TBSA, bacteremia with more than one organism, MDRO bacteremia, and bacteremia with *P aeruginosa* or *K pneumoniae* (Table 4). Bacteremia with *K pneumoniae* was a major risk factor for mortality on multivariate analysis (relative risk = 3.72; $p = 0.01$). Otherwise, age and ISS were the only other risk factors associated with mortality on multivariate analysis. Percent of TBSA burn was not a major predictor of mortality on multivariate analysis (see Table 4). Because of the small numbers associated with individual MDRO infections, outcomes comparison of individual MDRO pathogens was not performed.

There were 328 patients who required mechanic ventilation for a median of 5 days (range 1 to 206 days). Nonbacteremic patients requiring ventilator support (n = 243) were ventilated for a mean of 7.53 (median 3; range 1 to 100) days. Bacteremic patients requiring mechanic ventilation (n = 85) received a mean of 31.1 (median 15; range 2 to 206) days of support; a statistically significant increase versus the nonbacteremic group ($p \leq 0.001$). Among ventilated patients with bacteremia, those with *K pneumoniae* (n = 32) had considerably more days on mechanic ventilation: (mean 43.5 days; median 32 days; range 3 to 172 days) compared with those infected with other pathogens (n = 53; mean ventilator days 23.7; median 10 days; range 2 to 206 days). This difference was statistically significant ($p = 0.001$). Lastly, there was a statistically significant dif-

Table 3. Predictors of Mortality for All Study Patients (Bacteremic and Nonbacteremic)

Risk factor	Univariate			Multivariate		
	Relative risk	95% CI	p Value	Relative risk	95% CI	p Value
Age	1.03	1.02–1.05	<0.01	1.07	1.05–1.09	<0.01
TBSA burned (%)	1.09	1.07–1.10	<0.01	1.06	1.04–1.08	<0.01
Injury severity score	1.14	1.11–1.16	<0.01	1.07	1.03–1.11	<0.01
Bacteremia	18.6	11.1–31.1	<0.01	2.60	1.18–5.69	0.02
OIF/OEF versus non-OIF/OEF	0.92	0.57–1.47	0.72	NA	NA	NA

OEF, Operation Enduring Freedom (combat operations in Afghanistan); OIF, Operation Iraqi Freedom; TBSA, total body surface area.

Table 4. Predictors of Mortality for Bacteremic Burn Patients

	Univariate			Multivariate		
Risk factor	**Relative risk**	**95% CI**	**p Value**	**Relative risk**	**95% CI**	**p Value**
Age	1.03	1.00–1.06	0.03	1.06	1.02–1.09	<0.01
TBSA burned (%)	1.03	1.01–1.05	<0.01	NS	NS	NS
Injury Severity Score	1.05	1.01–1.08	0.01	1.08	1.03–1.13	<0.01
OIF/OEF versus Non-OIF/OEF	0.81	0.35–1.86	0.62	NA	NA	NA
Bacteremia with more than one organism*	1.92	0.82–4.53	0.14	NA	NA	NA
Multiple episodes of bacteremia	0.34	0.12–1.03	0.051	NS	NA	NA
Bacteremia with a MDRO	2.78	1.13–6.83	0.03	NS	NS	NS
Bacteremia with *Pseudomonas aeruginosa*	2.25	0.96–5.3	0.06	NA	NA	NA
Bacteremia with *Klebsiella pneumoniae*	2.71	1.14–6.49	0.03	3.72	1.3–10.6	0.01
Bacteremia with *Acinetobacter*	0.48	0.21–1.11	0.08	NA	NA	NA
Bacteremia with *Staphylococcus aureus*	0.79	0.30–2.06	0.63	NA	NA	NA

*Because the p value on univariate analysis approached significance, multivariate analysis was performed both including and excluding this factor in the model. In both instances, this term was removed from the final analysis by the backward conditional method and did not affect the analysis.
ISS, Injury Severity Score; MDRO, multidrug-resistant organism; NA, not analyzed in multivariate model; NS, not significant after multivariate analysis; OEF, Operation Enduring Freedom (combat operations in Afghanistan); OIF, Operation Iraqi Freedom; TBSA, total body surface area.

ference between bacteremic ventilated patients with non-MDRO bacteremias (n = 30, days on ventilator: mean 16.1; median 9; range 2 to 120) compared with ventilated patients with MDRO bacteremia (n = 55, days on ventilator: mean 39.4; median 22; range 2 to 206; $p \leq 0.001$). There were no statistically significant differences in the number of mechanic ventilation days required by those patients with *P aeruginosa*, Acb, or *S aureus* bacteremia ($p > 0.05$ for all).

Patients were stratified into TBSA groups as follows: TBSA < 30, TBSA 30 to 60, and TBSA > 60. Nonbacteremic patients with TBSA < 30 (n = 162) required ventilatory support for a median of 2 days (interquartile range [IQR] 1 to 7 days), but bacteremic patients in this stratum (n = 17) had a median of 8 days on the ventilator (IQR 3.5 to 18.5 days; p = 0.02). For the TBSA 30 to 60 stratum, nonbacteremic patients (n = 57) had a median of 5 days on the ventilator (IQR 2.5 to 11.5 days) compared with those with bacteremia (n = 42), with a median of 15 days on the ventilator (IQR 6.75 to 30.25 days; $p < 0.01$). Those nonbacteremic patients with TBSA > 60 (n = 23) had a statistically significantly lower number of ventilator days, with a median of 3 days (IQR 2 to 7 days) compared with bacteremic patients in this category (n = 26), with a median of 28.5 ventilator days (IQR 11.75 to 72.5 days; $p < 0.01$).

DISCUSSION

During OIF/OEF, > 28,381 military personnel have been wounded in action, of which 12,987 have not returned to duty.[5] Burn casualties make up approximately 5% of combat casualties in OIF/OEF. Combat burn patients differ from civilian burn patients in the mechanisms of their injuries. Combat burn patients are commonly younger, have a longer time from injury to admission to a burn center, have a higher ISS, and have a higher incidence of inhalation injury.[1] Mortality is not different between the two populations.

Since the onset of OIF/OEF, there has been a number of reports describing infections with multidrug-resistant bacteria, particularly Acb, developing in combat casualties.[6-8] Our earlier assessment of burn patients infected with Acb did not show attributable mortality.[4] In this assessment of bacteremia, including infections from multidrug-resistant bacteria, there was no difference in outcomes between those burned during combat operations versus those burned in the US. Bacteremia, whether caused by MDRO or not, was associated with increased mortality and prolonged ventilation. Although bacteremic patients were found to have longer times on mechanic ventilation than nonbacteremic patients, it was believed that this finding might have been a result of other factors, such as TBSA and ISS. When patients were stratified into TBSA ranges, an association of bacteremia and duration of ventilation was still present. In the TBSA > 60 stratum, a much smaller number of ventilator days was seen in the nonbacteremic group because of high early mortality in the hospital course. This early mortality resulting in a lower number of ventilation days in the nonbacteremic group was not found in the TBSA 30 to 60 stratum. This supports the hypothesis that bacteremia does prolong the number of ventilator days in this group. Median ISS for the bacteremic and nonbacteremic patients in the 30 to 60 TBSA stratum were the same (25 versus 25.5, respectively). When the bacteremic patient cohort was analyzed, only *K pneumoniae* bacteremia was associated with mortality and prolonged ven-

tilation on multivariate analysis. In general, TBSA and ISS can be factors in patients acquiring bacteremia, but they should not influence which organism causes the bacteremia. We do not believe, as a result, that TBSA and ISS were substantial confounders when analyzing this group of patients.

When analyzing all patients, bacteremic and nonbacteremic, TBSA is a substantial risk factor for mortality on both univariate and multivariate analysis. In the second analysis, where bacteremic patients alone were analyzed, TBSA was no longer a substantial risk factor for mortality in this group. A possible explanation for this finding is that the bacteremic cohort, as a group, had a larger TBSA (Table 1). By analyzing the subset with bacteremia, we are selecting patients with the larger burns, which would then decrease the impact of TBSA in the multivariate analysis.

The impact of multidrug-resistant bacteria and the potential lack of antimicrobial agents to adequately treat these infections is a global threat.[9] Although numerous pathogens have been responsible for causing sepsis among burn patients, *S aureus* and *P aeruginosa* have traditionally been the most common pathogens. In this study, *K pneumoniae* and Acb were also major pathogens associated with sepsis among burn patients. Overall, our gram-negative isolates were very resistant, and we used a stricter definition of multidrug-resistance for *P aeruginosa* because of background rates of resistance traditionally seen in our burn-unit isolates. There has been an increasing number of reports describing a change in the bacteriology of burn units around the world. In an autopsy series of burn patients from India, *P aeruginosa* and *Klebsiella* species were the pathogens most frequently recovered, but no cases of *S aureus* or Acb were described.[10] In a study performed in Brazil assessing bacteremia, the most common isolates recovered was *Staphylococcus,* followed by *Acinetobacter, Enterobacter cloacae,* and *K pneumoniae*.[11] It is unclear as to why there is a changing epidemiology of pathogens within burn units but, for Acb infections among OIF/OEF casualties, it appears that nosocomial transmission and patient transfers around the world play the predominate role.[12] It is also known that once these multidrug-resistant bacteria colonize burn units, it is very challenging to eradicate them.[13]

Only *K pneumoniae* had attributable mortality in this patient population, even when controlling for age, ISS, and TBSA, which are traditionally the patient characteristics that have the greatest influence on outcomes. It is unclear why *K pneumoniae* is associated with such mortality. There are a number of virulence factors associated with this pathogen, and recent descriptions of a more virulent strain associated with abscess production.[14,15] These strains are also frequently ESBL-producing and a recent report described the importance of initial antimicrobial therapy impacting patient outcomes.[16] This is likely not the case in our burn center, as we have been empirically using carbapenems, the drug of choice for ESBL-producing strains, since the onset of OIF/OEF, because of Acb infections.

Military personnel who are burned during support of OIF/OEF and become bacteremic do not have different outcomes than burn patients not associated with military operations. All burn patients have poorer outcomes if they are infected with multidrug-resistant bacteria. Among the top four organisms detected during episodes of bacteremia, *S aureus*, *P aeruginosa*, Acb, and *K pneumoniae*, we found only *K pneumoniae* to be associated with attributable morbidity and mortality. In centers where ESBL-producing *K pneumoniae* have been frequently recovered, initial therapy for sepsis in the burn-patient population should include coverage of these organisms. Additional work to elucidate the reason for this attributable morbidity and mortality needs to be undertaken.

Our study evaluated risk factors for mortality in our bacteremic burn-patient population, and the implication of being injured in OIF/OEF. We found that burn casualties of OIF/OEF did not have substantially different adverse outcomes versus patients not associated with these military operations. In addition, bacteremia is associated with increased mortality in burn patients, with *K pneumoniae* bacteremia having the most impact on mortality. Measures to reduce bacteremia in burn units as a result, should be implemented. Strict infection-control protocols and optimal central-line management should be enforced. Appropriate tailoring of empiric antimicrobials should be used to cover for multidrug-resistant organisms, especially ESBL *K pneumoniae*.

Author Contributions

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